Interagency Autism Coordinating Committee Meeting Minutes

July 15, 2008

The Interagency Autism Coordinating Committee (IACC) convened at 9:00 a.m. on July 15, 2008, in Conference Rooms E1 and E2 of the Natcher Building at the National Institutes of Health in Bethesda, Maryland, and adjourned at approximately 3:15 p.m.

In accordance with Public Law 92-463, the meeting was open to the public. Thomas R. Insel, M.D., Director, National Institute of Mental Health, chaired the meeting.

Committee Members Present at the Meeting: **Thomas R. Insel**, M.D., National Institute of Mental Health (NIMH), *Chair*; **Della Hann**, Ph.D., NIMH, *Executive Secretary*; **Duane F. Alexander**, M.D., National Institute of Child Health and Human Development (NICHD); **Ellen W. Blackwell**, M.S.W., Centers for Medicare and Medicaid Services (CMS); **Judith Cooper**, Ph.D. (representing **James F. Battey**), National Institute on Deafness and other Communication Disorders (NIDCD); **Margaret Giannini**, M.D., F.A.A.P., Office on Disability, U.S. Department of Health and Human Services (DHHS); **Lee Grossman**, Autism Society of America; **Gail R. Houle**, Ph.D., U.S. Department of Education (ED); **Yvette M. Janvier**, M.D., Children's Specialized Hospital; **Story C. Landis**, Ph.D., National Institute of Neurological Disorders and Stroke (NINDS); **Cindy Lawler**, Ph.D., National Institute of Environmental Health Sciences (NIEHS); **Christine M. McKee**, J.D.; **Patricia A. Morrissey**, Ph.D., Administration for Children and Families; **Lyn Redwood**, R.N., M.S.N., Coalition for SafeMinds; **Stephen M. Shore**, Ed.D., Autism Spectrum Consulting; **Alison Tepper Singer,** M.B.A., Autism Speaks; **Edwin Trevathan,** M.D., M.P.H., Centers for Disease Control and Prevention (CDC); **Peter van Dyck**, M.D., M.P.H., Health Resources and Services Administration (HRSA).

Call to Order and Opening Remarks

Thomas Insel welcomed the Interagency Autism Coordinating Committee and meeting observers to the National Institutes of Health and introduced Della Hann, the Director of the Office of Science Policy, Planning, and Communications at NIMH and the new Executive Secretary for the IACC. He also noted that the National Database for Autism Research (NDAR) had recently been updated and is accepting data from the NIH Autism Center of Excellence grantees.

Review and Approval: May 12, 2008 IACC Meeting Summary; Summary of Advances in ASD Research

After the members of the IACC introduced themselves, they voted unanimously to approve the draft minutes of the May 12, 2008 IACC meeting and the draft report, "Summary of Advances in Autism Spectrum Disorder (ASD) Research: Calendar Year 2007."

Report from the Services Subcommittee

Ellen Blackwell and Lee Grossman described the discussions from a meeting of the IACC Services Subcommittee, held on June 13, 2008 at the offices of the Autism Society of America in Bethesda, MD. The subcommittee reviewed the 41 research initiatives prepared at strategic planning workshops earlier in the year and determined that 13 were related to services. The subcommittee also prepared a request for information (RFI) on ASD-related services, which the IACC voted to approve and issue.

In addition, various plans were discussed by the subcommittee including holding a series of town hall meetings about services and supports, reviewing the roadmap prepared by the previous IACC to identify items that could be accomplished by the current IACC, surveying ASD-related services in individual states, developing models of services and supports for children and adults with ASD, and developing a website to convey research results to the public. Ms. Blackwell noted that CMS had recently issued a task order on specific areas of ASD-related services research.

Mr. Grossman indicated that the RFI and possible town hall meetings could provide input to the November IACC meeting, which Dr. Insel stated will focus on: 1) ASD-related services and supports, and 2) final approval of the Strategic Plan for ASD Research.

Report on Strategic Planning Workgroup Meeting

Judith Cooper described a meeting of the Strategic Planning Workgroup that reviewed the draft strategic plan. The meeting was held on July 8th as a webinar and conference call. A total of 76 people participated, including workgroup and IACC members (whose comments could be heard) and members of the public (who could listen to the discussion). The workgroup members offered comments and suggestions about many parts of the draft plan. No consensus was sought.

Several comments emphasized the need to enhance and clarify language to capture more effectively the values and goals put forth by the IACC. Other comments suggested strengthening the integration of cross-cutting themes and more effectively conveying the sense of urgency expressed by the IACC and the ASD community. Additional comments included emphasizing prevention, describing the need for cutting-edge science, highlighting early detection, embracing the heterogeneity in various aspects of ASD, and spotlighting the partnership between the ASD community and the research communities.

The workgroup also provided input on each of the six questions used by the IACC to organize the strategic plan: Question 1 - “When should I be concerned?”; Question 2 - “How can I understand what is happening?”; Question 3 - “What caused this to happen and can this be prevented?”; Question 4 - “Which treatments and interventions will help?”; Question 5 - “Where can I turn for services?”; and, Question 6 - “What does the future hold?” Dr. Cooper presented the workgroup suggestions for each of the six questions. Also, she noted that several workgroup members offered to participate in the next steps in the strategic planning process (i.e., identifying funding sources and mechanisms to support the research outlined in the strategic plan).

IACC Discussion of the Draft Strategic Plan for ASD Research

Following Dr, Cooper’s presentation, Dr. Insel led the IACC through a detailed discussion of each section of the draft plan to consider the comments from the workgroup. Key discussion points included:

Cross-cutting themes. Lyn Redwood praised the comments from the workgroup and asked that the cross-cutting themes be revised to include the recommendations of the workgroup. She recommended that the strategic plan include a greater focus on the environment, co-morbidities, multiorgan system impairment, and prevention. Alison Singer recommended a greater focus on earlier detection and intervention. Christine McKee noted that the need for greater resources should be emphasized. Dr. Insel emphasized the workgroup suggestion to add the need for innovative science to the introductory section, and the members agreed that the plan should be revised accordingly.

Regarding the workgroup recommendation to emphasize the importance of prevention in the strategic plan, Ms. Redwood and Ms. Singer urged including prevention in the vision or mission statement. Stephen Shore urged that the word "ethical" be inserted before "prevention." Dr. Shore said that the goal should be for people with autism to be healthy and lead fulfilling and productive lives to the fullest extent possible. Mr. Grossman added that the strategic plan should reiterate that all people with autism should be valued. Ultimately, the IACC agreed that the strategic plan should be revised to include a carefully worded cross-cutting theme on prevention that reflects the IACC's concerns and observations.

Ms. Redwood suggested that the combined influence of genetics and the environment be included as an additional cross-cutting theme or included as one of the existing themes to highlight the need to understand and mitigate environmental factors that contribute to ASD. The IACC members agreed.

I. When should I be concerned? The IACC discussed the aspirational goal that "All children with ASD will be identified at an early age." Several committee members said that "early age" was too vague, but suggestions to replace that phrase with a specific age raised objections that early detection of ASD in all cases would be unrealistic. However, several committee members noted that the plan's goals need to be bold to inspire action and to convey a sense of urgency. Story Landis and Duane Alexander suggested that specific ages be discussed in the research opportunities, which could convey a sense of progression over time and be more detailed. Yvette Janvier suggested revising the goal as, "Children with ASD will be identified at age two and receive care appropriate to diagnosis." Gail Houle suggested using "intervention" instead of "care" to indicate a proactive approach.

II. How can I understand what is happening? The members agreed to adopt most of the workgroup recommendations for this section, including expanding access to biospecimens to include other tissues beyond brain (e.g., skin fibroblasts), including youths and adults in a comprehensive large-scale study of development, and sharpening the focus on immune and metabolic interactions with the central nervous system. Ms. Redwood urged that the section be revised to highlight the research opportunities regarding immune issues and comorbidities. Dr. Insel agreed that the plan should emphasize how little is known about many aspects of ASD and that there are many opportunities for progress.

III. What caused this to happen and can this be prevented? Dr. Insel asked the IACC to clarify the extent to which the strategic plan should address the topic of vaccine research. Dr. Insel reported that he had been urged by workgroup members and other stakeholders to highlight vaccines in the plan, while other stakeholders and members expressed concern that too much attention is given to the topic of vaccines. Ms. Redwood said that the public comments received throughout the strategic planning process emphasized the importance of this topic. Cindy Lawler and Peter van Dyck proposed that vaccines be one of several possible environmental factors listed as needing further study. Also, Dr Alexander suggested

including language about monitoring issues of the possible association of vaccines and ASD to identify needs and opportunities; the members agreed.

The members also discussed a short-term objective under Question 3, "Establish consensus on at least three additional environmental factors as targets for study as potential causes of ASD by 2010." Ms. Redwood urged reaching consensus on the targets for study much sooner than 2010, and suggested that the Institute of Medicine (IOM) Report ("Autism and the Environment: Challenges and Opportunities for Research, Workshop Proceedings") serve as the basis for identifying which environmental factors should be studied. Ms. Redwood also urged the committee to make the objective more ambitious by focusing on more than three environmental factors. Dr. Alexander suggested that the objective be revised to focus on initiating the studies, and the members agreed.

Mr. Grossman suggested adding "recovery" to the goal regarding prevention, and Dr. Insel agreed.

IV. Which treatments and interventions will help? Based on the recommendations from the workgroup, the IACC agreed to add more emphasis on school-age, adolescence, and adulthood and increase the number of studies on treatments in current use by parents and families. Ms. Redwood urged the committee to support a more ambitious objective regarding randomized control trials addressing co-occurring medical conditions. She suggested that the objective be to conduct five or ten studies on that topic by 2010. Dr. Landis cautioned against engaging parents and families in clinical trials that are not likely to be helpful. Discussion ensued about the number of trials needed, with IACC members in general agreement that at least three to five trials would be appropriate for this objective.

V. Where can I turn for services? The workgroup recommended revising this section significantly, and the IACC agreed. Adopted changes include a revision of the aspirational goal and replacement the information about the prevalence of ASD with information about ASD services and communities of care.

VI. What does the future hold? Regarding the aspirational goal for this section, Ms. Blackwell noted that the term "public understanding" was unclear. Ed Trevathan emphasized that the public needs to be aware of the ability of people with ASD to make great contributions. Ms. Blackwell also recommended that the "What Do We Need" section include oral health as an important outcome of interest for adults with ASD.

Dr. Insel stated that the staff would incorporate the IACC comments into the strategic plan and return a new draft to the IACC for review and approval.

IACC Discussion of Next Steps for Finalizing the Strategic Plan

Dr. Hann then presented options for finalizing the strategic plan, including obtaining public comment on the draft plan, forming a strategic planning implementation workgroup, and adhering to a timeline for the plan's completion.

Public comments. Dr. Hann outlined several ways for gathering public input once the IACC has approved a draft plan for public dissemination. A Request for Information (RFI) could be issued along with dissemination of the draft plan; town hall meetings could be held to discuss the plan; smaller focus groups could be convened to discuss the

plan; or web-based input could be gathered through such means as webinars. Regardless of how the information was gathered, it would be summarized and made public.

Ms. Blackwell suggested using the RFI process because it gives everyone a chance to comment. Ms. McKee suggested using focus groups to create a two-way conversation with the public. Ms. Singer noted that webinars also can result in two-way conversations while involving much larger and more dispersed groups. Dr. Lawler favored a general strategy for two-way and diverse communications because it would serve the both short-term needs and long-term objectives of the IACC. Dr. Insel proposed that a long-term plan be developed for getting input and communicating with the public in a clear and transparent manner.

Implementation workgroup. Dr. Hann proposed that the IACC form an implementation workgroup to recommend budgetary requirements for the strategic plan, consider issues of accountability in implementing the plan, suggest milestones and timelines for progress, and the consider various means of reviewing and funding proposed research. Dr. Hann suggested possible federal agencies and private organizations to be included in the workgroup and suggested that the group meet in closed session, which could help separate discussions of funding from discussions of who would perform needed research. She recommended that the workgroup include people who have experience in developing budgetary estimates for proposed research.

Ms. Blackwell said that the workgroup should include a person or persons with ASD, a family member of a person with an ASD, and a representative from the Department of Education. Ms. Redwood asked if the workgroup that commented on the draft strategic plan could be reconvened to develop budgetary requirements. Judith Cooper stated that some members of the current group would have conflicts of interest because they would be likely to respond to the research funding initiatives. Dr. Insel emphasized that members of the implementation workgroup needed to have experience and expertise in estimating the cost of research and identifying the best funding mechanisms for performing research.

Ms. Redwood suggested that the Autism Society of America be represented on the workgroup, but also urged the committee to set priorities before embarking on implementation. Dr. Insel commented that his understanding what that the IACC had decided to retain all of the proposed research initiatives in the strategic plan and each would be prioritized as either a short- or long-term objective.

Ms. Singer suggested expanding the workgroup charge to include coordination of funding so that a diversity of research projects and performers could be supported. Dr. Insel observed that some coordination will result from an ongoing review of the strategic plan by representatives from various federal agencies. Dr. Landis pointed out that the workgroup also could identify research projects that have not been effective and help shift funding from those projects into more productive areas. Ms. Redwood called for a re-engineering of the funding process, including the greater involvement of stakeholders, so that very high priority research projects can be undertaken.

Mr. Grossman stated that he was uncomfortable with the proposed workgroup because it could be unduly influenced by organizations with a vested interest in the proposed research rather than tapping into unused resources that could make important

contributions to ASD-related research. Dr. Insel responded that representation from such organizations could provide valuable input to the IACC.

Dr. Janvier moved that such a workgroup be formed with the inclusion of a person with ASD, a family member of a person with ASD, and a representative from the Department of Education. The committee voted in favor of the motion, with two committee members voting against it.

Timeline. Regarding the timeline for the plan's preparation, Dr. Hann proposed completing the public comment period on the draft strategic plan by the end of September. Simultaneously, the implementation workgroup could be developing budgetary requirements for the research contained in the plan. Then, the IACC could consider a final draft plan as part of its meeting in November 2008.

Ms. Redwood asked if not just the summaries of IACC meetings but the complete transcripts could be posted on the web, and Dr. Hann responded that she would check on the legal requirements for such postings.

Science Update: From Gene to Pathophysiology to Treatment in a Developmental Brain Disorder

After lunch, Dr. Insel introduced Mark Bear, who is Director of the Picower Institute for Learning and Memory and a professor of neuroscience at the Massachusetts Institute of Technology. Dr. Bear pointed out that proper brain function requires precise connectivity between neurons. Diseases known collectively as synapsopathies can result in disrupted connectivity during the brain's development and functioning. In particular, synapses that use glutamate as a transmitter are the most common mediator of synaptic activity in the brain, and the role of these synapses both in normal development and in disease is a very active area of inquiry.

Modification of synapses requires the synthesis of proteins within neurons. Therefore, a variety of biochemical systems closely couple synaptic activity in the brain to the synthesis of new proteins. The synthesis of too much protein or too little protein can disrupt neuronal development and functioning. In the case of fragile X syndrome, a protein known as FMRP is missing from neurons because of the silencing of a gene known as FMR1. FMRP acts to down-regulate protein synthesis in the brain, so when it is missing, too much protein is synthesized. This results in a variety of abnormalities in the brain, testes, and other parts of the body. About 20 to 30 percent of the children with fragile X syndrome satisfy the full diagnostic criteria for autism, and fragile X accounts for about 5 percent of autism cases. This research may provide critical insight into understanding how brain function altered by genetic mutation may lead to an ASD.

The identification of the gene that produces FMRP and the biological mechanism responsible for fragile X has made it possible to explore ways of preventing and treating the syndrome. Compounds that reduce the synthesis of protein have corrected many aspects of fragile X syndrome in model organisms such as mice, fish, and flies. Recently, pharmaceutical companies have initiated human clinical trials of drugs that slow protein synthesis to treat fragile X syndrome.

Mutations in other genes involved in the regulation of protein synthesis also produce disorders related to autism. For example, mutations in the gene responsible for tuberous sclerosis have recently been treated in mice with a drug that inhibits the synthesis of particular proteins. Furthermore, a recent study found that many genetic deletions and variations that appear to

contribute to the development of autism are involved in the regulation of protein synthesis in the brain.

In response to a question from Ms. Singer, Dr. Bear said that drugs designed to treat fragile X syndrome in model animals have beneficial effects even when given to adults. Dr. Insel added that several recent studies have seen similar beneficial results when young adults with different disorders are treated for syndromes that cause cognitive impairment.

Science Update: Report from the Workshop, Mitochondrial Encephalopathies: Potential Relationships to Autism?

Walter Koroshetz, Deputy Director of the National Institute of Neurological Disorders and Stroke (NINDS), summarized the discussions that occurred during a symposium held on June 29, 2008 in association with the annual meeting of the United Mitochondrial Disease Foundation (see http://www.ninds.nih.gov/news_and_events/proceedings/20090629_mitochondrial.htm for more information about the workshop proceedings). There is an intriguing overlap between mitochondrial disorders and autism, Dr. Koroshetz said. The synaptic activity of the brain is a major consumer of energy in the body, while the mitochondria in cells are the body's main source of energy. Mitochondria also are involved in many other cellular processes, such as the storage of calcium, and they are related to the process of cell death. Therefore, mitochondrial defects can result in a wide variety of pathological conditions.

There are very few definitive tests for many kinds of mitochondrial dysfunctions. The causes and course of mitochondrial diseases vary greatly from person to person, and the same mutations in DNA related to mitochondrial function can have different outcomes in different people. Biochemical tests for indicators of mitochondrial function can vary from one laboratory to another. Some tests, such as biopsies of various tissues, can be extremely invasive. The existence of a mitochondrial disorder can be difficult to prove even when it is strongly suspected.

Mitochondrial disorders can be caused by triggers such as viral infections or interactions with drugs. For example, Reye's syndrome is thought to result from a loss of mitochondrial function after an infection. Researchers are investigating whether dysfunctions in mitochondria can lead to other diseases, such as Parkinsons or Huntingtons.

Attendees at the symposium discussed potential ties between known mitochondrial disorders and autism. Some families with mitochondrial disorders also have children with autism. Some of the genes found to be associated with autism are involved in mitochondrial function. The group discussed reports of mitochondrial dysfunction in autism and noted that there has not yet been a compelling link except in rare cases with both a mitochondrial mutation and autism.

Ms. Redwood asked about the dietary supplements that parents and physicians use to counter mitochondrial disorders, which some parents also administer to their autistic children. Dr. Koroshetz noted that several of these supplements have been or are being investigated, but randomized controlled studies have been inconclusive. Nevertheless, most of the doctors who treat children with mitochondrial disorders use supplements aggressively and try to prevent circumstances that can put stress on mitochondria, such as dehydration or infection.

Ms. Redwood also asked whether vaccines could be potential triggers for mitochondrial disorders. Dr. Koroshetz responded that physicians who treat children with mitochondrial disorders are highly concerned that children avoid infections that can exacerbate their conditions, so they generally recommend a full set of vaccines.

Dr. Landis asked whether there might be any test for mitochondrial function right after birth or during the initial well-baby checkups. Dr. Koroshetz responded that the only definitive test would be searching for a mutation in DNA affecting mitochondrial function. Dr. Trevathan, who was also at the symposium, added that some attendees were concerned that large numbers of children not be submitted to invasive procedures to look for mitochondrial disorders and that better screening techniques are needed to determine which children should undergo such procedures.

Public Comments

Kelli Ann Davis, the Washington, D.C., political liaison for Generation Rescue, read from a letter to HHS Secretary Michael Leavitt from the Subcommittee on Investigation and Oversight of the Committee on Science and Technology. The letter urged the IACC to promote a balanced research portfolio when examining the underlying causes of ASD. Without an understanding of the different causes for ASD, it will be difficult both to pinpoint genetic factors in ASD and to understand the role that environmental influences play in ASD. The letter also urged HHS to involve as many people as possible from the activist community in the decision-making process and to form a secretarial-level autism advisory board that could provide additional feedback to the department and serve as a liaison between the department and parents, individuals with ASD, and advocacy groups.

Margaret Dunkle, a senior fellow with the Center for Health Services Research and Policy at George Washington University, spoke about her nephew's daughter, Hannah Poling. She said that evidence strongly suggests that at least 4 to 5 percent, and perhaps as many as 20 to 30 percent, of children with autism have mitochondrial dysfunction. She recommended, among other steps, that the federal government create a new basic research program focused on mitochondrial dysfunction and neural inflammation in autism and other disorders, find ways to screen for and identify children susceptible to vaccines or other adverse events, support studies of the sibling of children with ASD, test alternative vaccine schedules and frequencies through the National Children's Study, launch a nationwide initiative to spot children who may be sensitive to vaccines, strengthen the vaccine adverse event reporting systems, reform vaccine practices to ensure that they are as safe as possible, update the vaccine injury compensation program, and improve federal oversight of vaccines.

James Moody, a director of the National Autism Association, summarized the key points from two letters directed to the IACC. He urged that a comprehensive analysis of the costs of ASD be conducted, that multiple studies of possible environmental contributors to ASD be conducted, that research on vaccines be included in the strategic plan, and that the strategic plan acknowledge that new cases of ASD have been rising. He also asked that public participation in decisions related to ASD be increased.

Closing Remarks

Dr. Hann asked IACC members to send their remaining suggestions regarding the draft strategic plan to her within a week's time so they can be incorporated into the next version of the plan. Dr. Insel thanked all of the attendees at the meeting for participating, and the meeting was concluded.